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ORIGINAL ARTICLE

Correlation of Apparent Diffusion Coefficient to cognitive impairment in Relapsing remittent multiple sclerosis (plaque, peri-plaque and Normal appearing white matter)

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Abstract The purpose of this study was to determine diffusion coefficient (ADC) in plaque, peri-plaque and normal-appearing white matter (NAWM) in multiple sclerosis (MS), compare them with the control and correlate findings with cognitive state.

Subjects and methods: Sixty-five participants were included and categorized into MS patients with normal cognition ($n = 25$); MS with mild cognitive impairment ($n = 20$) and control group (no MS and normal cognition; $n = 20$). The Montreal Cognitive Assessment was used to determine cognitive state. Mean ADC was measured in plaque, peri-plaques and NAWM, compared with ADC from corresponding white matter in control and correlated with cognitive scores. Chi Square and Pearson correlation coefficient were used.

Results: The mean ADC of peri-plaque and NAWM in MS group with cognitive impairment was significantly higher than MS group with normal cognition ($p < 0.001$) and control group ($p < 0.05$) respectively. In MS patients with impaired cognition, the mean ADC in peri-plaque and NAWM demonstrated inverse correlations with cognitive state ($r = -0.64$, $p < 0.001$) and ($r = -0.56$, $p = 0.01$) respectively.

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Conclusions: ADC values in peri-plaque and NAWM have an inverse correlation with cognition in MS. The ADC is useful for detecting subtle abnormalities in white matter and can be used as a predictor of cognitive state.

1. Introduction

The characteristic abnormalities of multiple sclerosis (MS) in the brain consist of multiple white matter lesions (plaques) with high signal intensity (SI) on fluid attenuation inversion recovery (FLAIR), Proton density (PD) WI, and T2-WI and low SI on T1-WI. Lesions are found predominantly in a periventricular distribution, centrum semioval, and the calloso-septal interface. Additional sites of involvement include other parts of the cerebral white matter such as the subcortical white matter, optic nerves, corpus callosum, internal capsule, cerebellar peduncles, brainstem, and spinal cord (1).

Demyelinating lesions appear smaller on T1-WI than on T2-WI. Occasionally, they show a hyperintense border on T1-WI. Lesions in MS can be small, large, or confluent. The typical configuration is that of an ovoid lesion extending perpendicularly from the ventricular surface (Dawson's finger). This probably reflects the perivascular inflammation along a penetrating medullary vein. Atypical lesions and mass-like lesions occur with sufficient frequency to cause diagnostic errors (1).

Recent years have witnessed increasing interest in the prediction of neuropsychological (NP) impairment in patients with MS. Approximately 50% of MS patients exhibit some degree of NP impairment. Deficits in processing speed, memory, and higher executive function are particularly common, affecting the quality of life and employment (2).

A cognitive impairment substantially impacts the lives of patients with MS and their families. More than 50% of people with MS are unemployed within ten years of diagnosis (3).

Identifying patients at risk for NP disabilities on the basis of MRI would enhance the quality of care. It is also increasingly recognized that early microstructure changes in the normal-appearing brain tissue (NABT) may also predict cognitive impairment in MS (4).

Diffusion-based imaging techniques, particularly diffusion-weighted imaging (DWI) and diffusion-tensor imaging (DTI), provide measures of increased pathologic specificity over conventional MRI. They are able to assess in vivo the presence of tissue damage occurring outside visible lesions, in the so-called normal-appearing tissue (5).

Diffusion techniques measure the random movement of water molecules in all tissues and fluid. Enhancement of such movement in brain parenchyma probably reflects the destruction of cell membranes, and in the case of MS, demyelination, and microscopic cell damage. Numerous studies have found increased translational movement of water in both active lesions and NABT in MS samples. As a result, diffusion-related measures may account for clinical signs independent of variance explained by more conventional, macroscopic MRI measures (6).

The purpose of this study was to utilize DWI and ADC values as a marker for early detection of MS patients susceptible to cognitive impairment and determine the most correlated sites (plaque, peri-plaque or normal-appearing white matter (NAWM)) for early prediction of cognitive impairment and to explore the correlation between water diffusion and cognition state.

2. Subjects and methods

This prospective study was carried out during the period from December 2014 to July 2015 in Radiology and Psychiatry department, Zagazig University, and included 45 MS patients and 20 matched age healthy volunteers as a control. Approval for the study from ethics committee board of our institute was taken, as well as, a written consent from all participants after explanation of the procedure.

2.1. Subjects

Forty-five patients (15 males and 30 females; mean age 34.22 ± 7.09 year) with a clinical and radiologic diagnosis of MS according to the McDonald criteria (7) were included in the study. The duration of clinically evident disease was 2–11 y (mean 4.89 ± 2.6) at the time of imaging and the number of attacks ranged from 2 to 7.

Inclusion criteria: Relapsing remittent MS patients with no relapse for at least 3 months before the study.
Exclusion criteria: (1) MS patient in active stage; (2) Other intracranial pathology; (3) psychotic patients; (4) Other major medical conditions or substance abuse; (5) Patients on antidepressants psychoactive steroids, or immunosuppressive drugs; (6) Patients with delirium; (7) The presence of any contraindications to MRI examination.

The control group 20 healthy volunteers (6 males, 14 females, mean age 35.4 ± 6.12 years) with no neurologic disability or intracranial pathology proved by clinical and conventional MR examination were included.

All the patients (n = 45) and the controls group (n = 20) underwent cognitive state assessment and MR examination including conventional MR imaging, DW-MR imaging, and its corresponding ADC map.

2.2. Cognitive state assessment

The Montreal Cognitive Assessment (MOCA) (8) was designed as a rapid screening reference for mild cognitive impairment. It is sensitively widespread and more easily used. MOCA assesses different cognitive domains: visuospatial/exec-

utive functions, naming, attention, concentration, language, abstraction, memory (delayed recall) and orientation.

2.2.1. Criteria for mild cognitive impairment

Time to administer the MOCA was approximately 10 min. The total possible score was 30 points; a score of 26 or above was considered normal. We added one point for an individual, who has 12 years or fewer of formal education. The cognitive state was assessed by MOCA scale for all MS patients and control group.

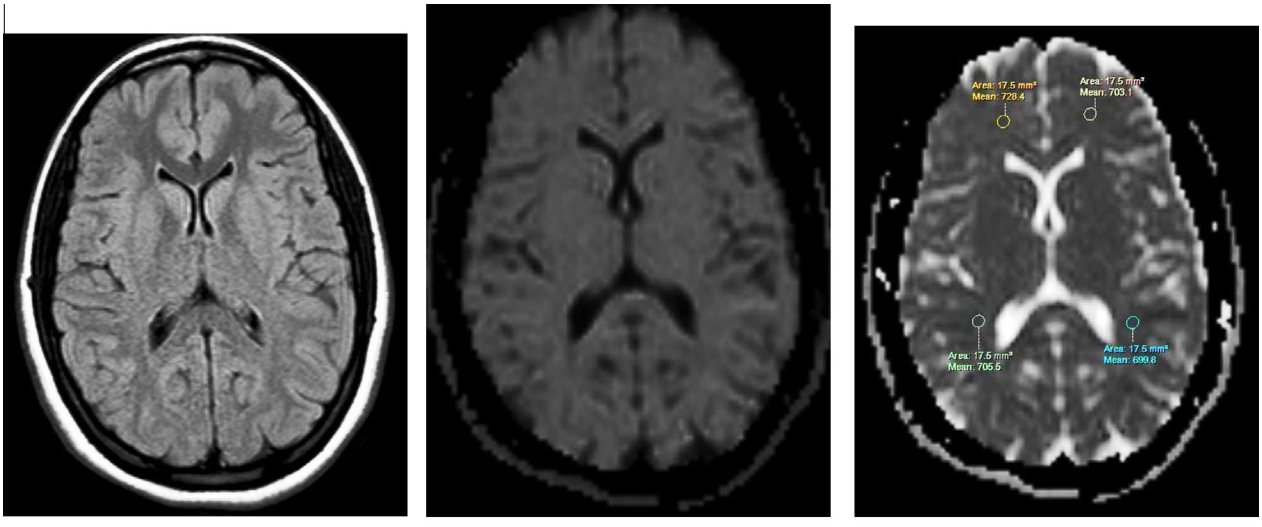
2.3. MRI examination

All MRI studies were done using 1.5 T MR Scanner (Achieva, Philips Medical System). Both patients and control groups were asked to get rid of any metallic subjects and they were informed about the duration of the examination, the position of the patient and the importance of being motionless. We used a head coil had an inner diameter of 27 cm.

- *Conventional magnetic resonance imaging (MRI):* The conventional MR sequences were done as the following: (1) Sagittal T1WI as localizer (TE 8/TR 500). (2) Axial T1WI (TR148-597/TE2-15). (3) Axial and Sagittal T2WI (TR4400-4800/TE110). (4) Axial FLAIR (TR6000/TE120-TI2000). (5) Coronal FLAIR (TR6000/TE120-TI2000). Section thickness = 5 mm, gap 1 mm. Field of view (FOV) = 240 mm in axial images and 30 mm in coronal images Matrix 320 × 224.
- *Diffusion-weighted MR imaging (DWI):* The imaging sequence for DWI was a multi-section single shot spin echo EPI sequence (TR/TE/NEX: 4200/140 ms/I). The diffusion gradients were applied sequentially in three orthogonal directions (thickness 5 mm, FOV 240 mm, a gap of 1 mm, and a matrix of 128 × 256). The total acquisition time was 80 s. We selected b values of 0 and 1000 s/mm^2 for the calculation of ADCs. The reconstructed magnitude images were transferred to the workstation for the calculation of the ADC values. The results of ADC values were described as mean ± SD in units of 1×10^{-3} mm^2/s.

2.4. Image analysis

All plaques were chronic and display isointense or hypointense signal on T1-weighed images and hyperintense on T2-weighed and FLAIR images without contrast enhancement. The NAWM was defined as area of white matter displayed normal signal in all pulse sequences of the conventional MR imaging. ROI fromT2-weighted and FLAIR images was copied and pasted onto ADC mapping images by the software system provided with the MR equipment.



(A) (B) (C)

Fig. 1 32 years old female healthy control subject with MOCA score 28. (A) FLAIR, (B) DWI, and (C) ADC showed normal white matter signal intensity. Quantitative ADC values of NAWM were 0.7284×10^{-3}, 0.7055×10^{-3}, 0.7031×10^{-3}, and 0.6998×10^{-3} mm^2/s.

Table 1 Demographic distribution between 3 groups.

	MS group with normal cognition (25)	MS group with cognitive impairment (20)	Control (20)	*p*
Age: Mean ± SD	34.8 ± 7.4	33.5 ± 6.7	35.4 ± 6.12	0.63 NS
Sex: Male:female	17:8	13:7	14:6	0.94 NS

NS: non-significant.

Table 2 Comparison between MS patients with cognitive impairment and MS patients without cognitive impairment as regards MOCA scores in our study.

Cognitive function	MS without CI 20 Mean ± SD	MS with CI 25 Mean ± SD	Control group 20	F	*p*	LSD
1 – Visuospatial/Executive						
A – Trail making test (Executive functions	0.95 ± 0.2	0.72 ± 0.1	0.95 ± 0.2	14.34	< 0.001**	< 0.001*,a 1[b] < 0.001*,c
B – Visuo-constructional skill (cube)	0.90 ± 0.4	0.56 ± 0.4	0.90 ± 0.4	5.56	0.006**	0.007*,a 1[b] 0.007*,c
C – Visuo-constructional skill (clock)	2.85 ± 0.6	2.16 ± 0.7	2.90 ± 0.61	7.49	0.001**	0.001*,a 0.79[b] < 0.001*,c
Total Range	4.7 ± 1.2 0–5	3.44 ± 1.1 0–5	4.75 ± 1.2 0–5	9.41	< 0.001**	< 0.001*,a 0.90[b] < 0.001*,c
2 – Naming (X ± SD) Range	2.70 ± 0.6 0–3	2.12 ± 0.4 0–3	2.90 ± 0.62 0–3	12.95	< 0.001**	< 0.001*,a 0.31[b] < 0.001*
3 – Attention						
A – Forward digit span (sustained attention) Range	0.95 ± 0.37 0–1	0.68 ± 0.28 0–1	0.95 ± 0.37 0–1	4.91	0.01**	0.008*,a 1[b] 0.008*,c
B – Backward digit span (sustained attention) Range	0.95 ± 0.2 0–1	0.80 ± 0.27 0–1	0.95 ± 0.22 0–1	3.13	0.05*	0.04*,a 1[b] 0.05*,c
C – Vigilance (concentration) Range	0.95 ± 0.16 0–1	0.80 ± 0.14 0–1	0.95 ± 0.2 0–1	6.25	0.003**	0.002*,a 1[b] 0.005*,c
D – Serial 7 s (working memory) Range	2.85 ± 0.45 0–3	2.32 ± 0.42 0–3	2.90 ± 0.5 0–3	11.51	< 0.001**	< 0.001*,a 0.74[b] < 0.001*,c
Total Range	5.70 ± 0.84 0–6	4.6 ± 0.76 0–6	5.75 ± 0.86 0–6	14.63	< 0.001**	< 0.001*,a 0.85[b] < 0.001*,c
4 – Language (repeat and fluency) (X ± SD) Range	2.20 ± 0.5 0–3	1.32 ± 0.4 0–3	2.30 ± 0.5 0–3	31.15	< 0.001**	< 0.001*,a 0.53[b] < 0.001*,c
5 – Abstraction (X ± SD) Range	1.80 ± 0.5 0–2	1.2 ± 0.4 0–2	1.85 ± 0.5 0–2	14.02	< 0.001**	< 0.001*,a 0.75[b] < 0.001*,c
6 – Delayed recall (X ± SD) Range	3.95 ± 1.16 0–5	3.16 ± 1.1 0–5	4.05 ± 1.17 0–5	4.21	0.02*	0.02*,a 0.81[b] 0.01*,c
7 – Orientation (X ± SD) Range	6 ± 0	6 ± 0	6 ± 0	–	–	–
8 – Total score (X ± SD)	27.05 ± 2.3	21.84 ± 2.2	27.70 ± 2.3	46.48	< 0.001**	< 0.001*,a 0.38[b] < 0.001*,c

*$p \leqslant 0.05$ (significant); **$p \leqslant 0.01$ (highly significant).
[a] MS without cognitive versus MS with cognitive.
[b] MS without cognitive versus control.
[c] MS with cognitive versus control.

The signal intensity values were noted according to each location as plaque, peri-plaque (within 1 cm of the plaque) and NAWM (far remote from the peri-plaque) (9). The images are obtained with a *b* value of 1000 s/mm^2. The independently placed regions of interest (ROI) were assessed in the plaque (in two different plaques), peri-plaque (in two different regions) and NAWM (periventricular in frontal and occipital regions).

At each pre-specified sites, two ADC values were obtained by using (average areas of regions of interest ROI = 16.4 ± 1.8 mm^2). Mean values were used for statistical comparisons. In control groups, the mean ADC values from the four

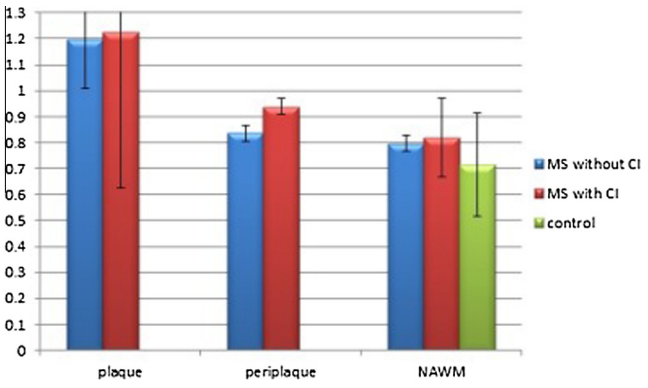


Fig. 2 Bare chart representing mean ADC values of plaque, periplaque and NAWM in the three groups.

NAWM regions corresponding to the NAWM in MS patients were calculated (Fig. 1).

2.5. Statistical analysis

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 18 (10). Qualitative data were represented as frequencies and relative percentages. To calculate the difference between qualitative variables we used Chi-square test. Quantitative data were expressed as mean ± SD (Standard deviation). To calculate the difference between quantitative variables in two groups in normally distributed data we used independent *T*-test.

An analysis of variance ANOVA *F*-test test was used to calculate the difference between quantitative variables in more than two groups in normally distributed data.

Pearson correlation coefficient was used to calculate the correlation between quantitative variables. We considered (+) sign as an indicator of direct correlation and (−) sign as an indicator of inverse correlation, and also, we considered values near to 1 as strong correlation and values near 0 as weak correlation.

The significance Level for all above-mentioned statistical tests was done. The threshold of significance is fixed at 5% level (*p*-value).

3. Results

Forty-five MS patients and 20 normal healthy control subjects participated in this study. The mean age of the participant and the gender distribution showed no significant differences between groups ($p = 0.63$, $p = 0.94$ respectively). Demographic characteristics of the study groups are summarized in Table 1.

3.1. Assessment of the cognitive functions

According to MOCA score all control subject had normal cognition (above 26) with their mean MOCA score 27.70 ± 2.3. Twenty-five cases (55.6%) out of the 45 MS patients had normal cognition with mean MOCA score 27.05 ± 2.3; however, the other 20 (44.4%) patients had a cognitive impairment with mean MOCA score 21.84 ± 2.2. In MS with cognitive impairment group all the cognitive functions (visuospatial, executive, attention, memory, fluency and orientation) were impaired with a significant *p*-value (Table 2). According to ANOVA test, there was a significant difference between MS patients with cognitive impairment and the other two groups (control and MS patients without cognitive impairment) as regards MOCA scores (Table 2)

3.2. Mean ADC values of plaque, peri-plaque and NAWM

The mean ADC value of the plaque in the two MS groups (impaired and normal cognition) was the highest ($1.198 \pm 0.19 \times 10^{-3}$ mm^2/s and $1.225 \pm 0.6 \times 10^{-3}$ mm^2/s

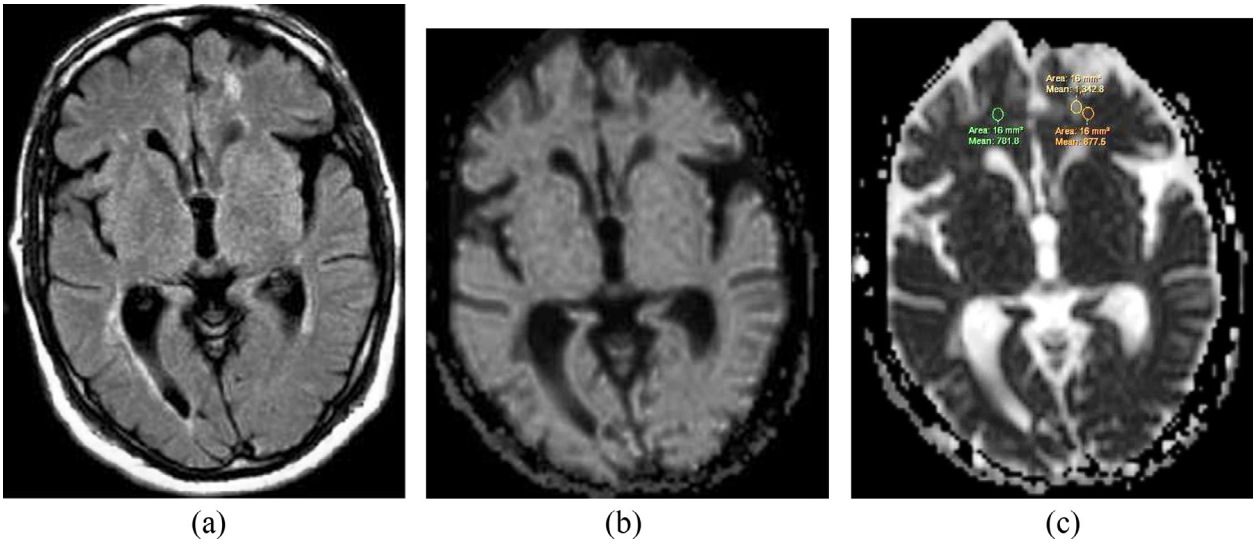


Fig. 3 28 years-old Female patient with RRMS (4 years duration) and normal cognition (MOCA score 27). (a) Axial FLAIR showed multiple plaques, (b) DWI image showed signal intensity of facilitated diffusion, (c) ADC map showed the following readings: Plaque 1.3428×10^{-3}, Periplaque 0.8775×10^{-3}, and NAWM 0.7928×10^{-3}, 0.7818×10^{-3} mm^2/s.

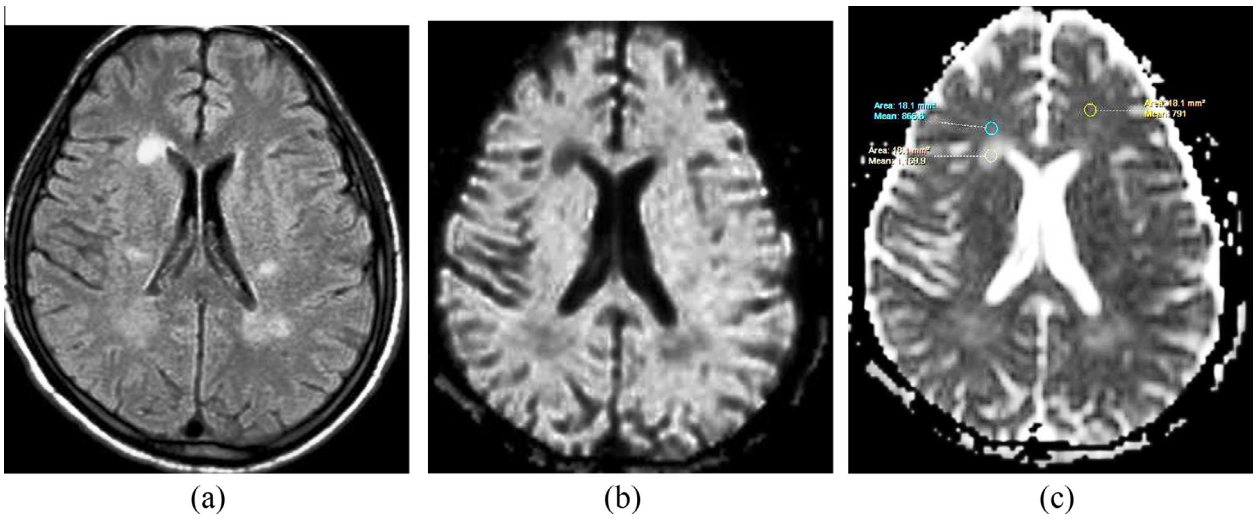


Fig. 4 37 year-old male with RRMS, no relapse for 9 months and no cognitive impairment (MOCA score 28). (a) Axial FLAIR showed multiple plaques, (b) DWI image showed signal intensity of facilitated diffusion, (c) ADC map showed the following readings: Plaque1.1699 $\times 10^{-3}$, Periplaque 0.8656 $\times 10^{-3}$, and NAWM 0.791 $\times 10^{-3}$ mm^2/s.

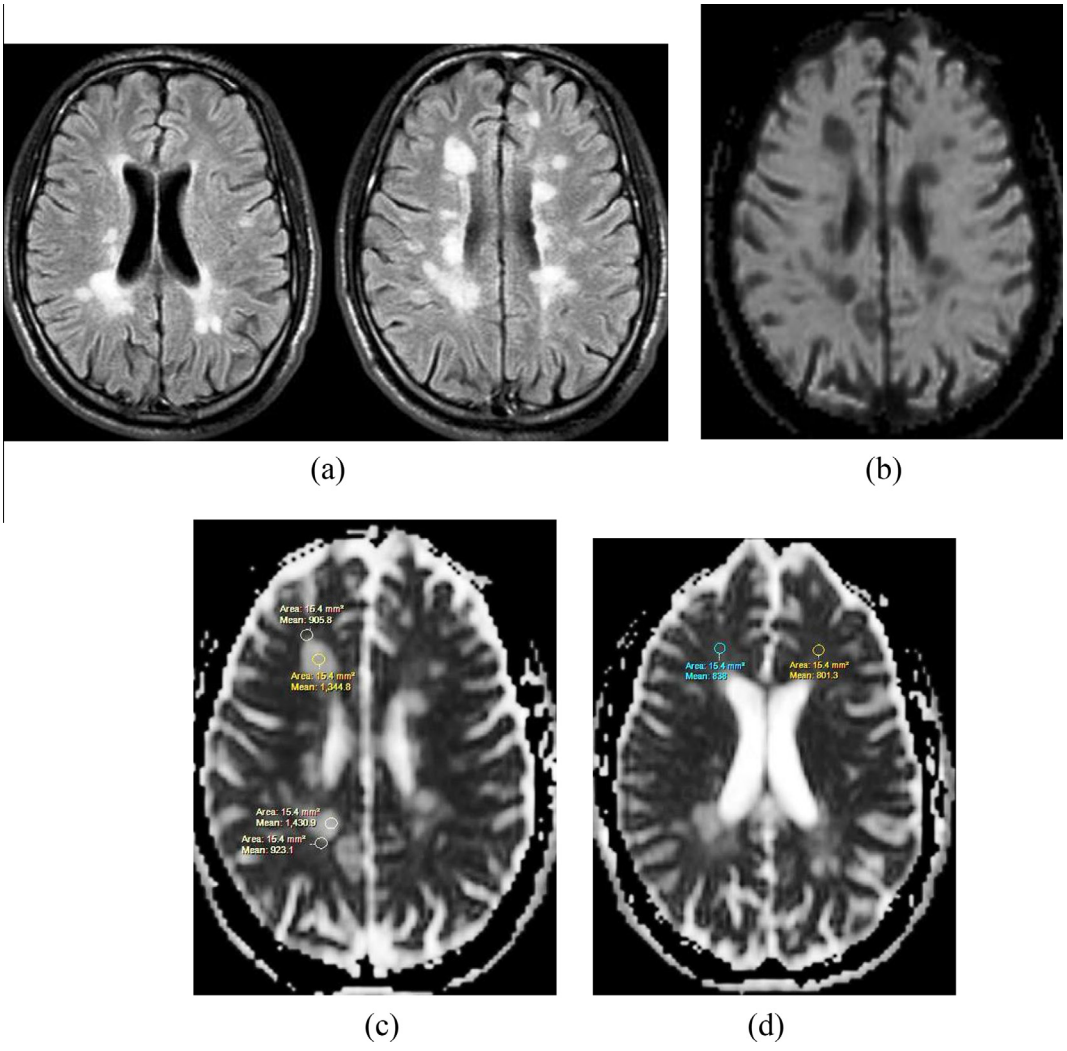


Fig. 5 38 year old female patient with RRMS and no relapse for 11 months with mild cognitive impairment (MOCA score 23). (a) Axial FLAIR showed multiple plaques, (b) DWI image showed signal intensity of facilitated diffusion, (c) ADC map showed the following readings: Plaque 1.4309 $\times 10^{-3}$, Periplaque 0.9231 $\times 10^{-3}$ and NAWM in image, (d) were 0.838 $\times 10^{-3}$ & 0.8013 $\times 10^{-3}$ mm^2/s.

respectively) with a significant difference ($p < 0.001$) between plaques and each of the peri-plaque and NAWM (Fig. 2).

Also, the mean ADC values of peri-plaque in MS group with cognitive impairment $0.939 \pm 0.03 \times 10^{-3}$ mm^2/s (Figs. 5 and 7) were significantly higher ($p < 0.001$) than those of MS group with normal cognition $0.837 \pm 0.03 \times 10^{-3}$ mm^2/s (Figs. 3 and 4 and 6). The mean ADC values of plaque, peri-plaque and NAWM of the three groups were demonstrated in Table 3.

The mean ADC values of NAWM in MS with impaired cognition $0.819 \pm 0.15 \times 10^{-3}$ mm^2/s were higher than MS with normal cognition $0.7962 \pm 0.03 \times 10^{-3}$ mm^2/s and control groups $0.7154 \pm 0.2 \times 10^{-3}$ mm^2/s (Table 3). It was significantly higher in MS patient with cognitive impairment (Figs. 5 and 7) than the control group ($p < 0.05$); however, there was no significant difference between both MS groups ($p < 0.51$), nor between normal cognitive MS patients and control group ($p < 0.08$).

3.3. Correlation between ADC values and MOCA scores

The MS group with impaired cognition demonstrates a significant inverse correlation between the mean ADC values of the peri-plaque region and MOCA scores ($r = -0.64$, $p < 0.001$). The less significant inverse correlation was found between the mean ADC values in the NAWM and MOCA scores

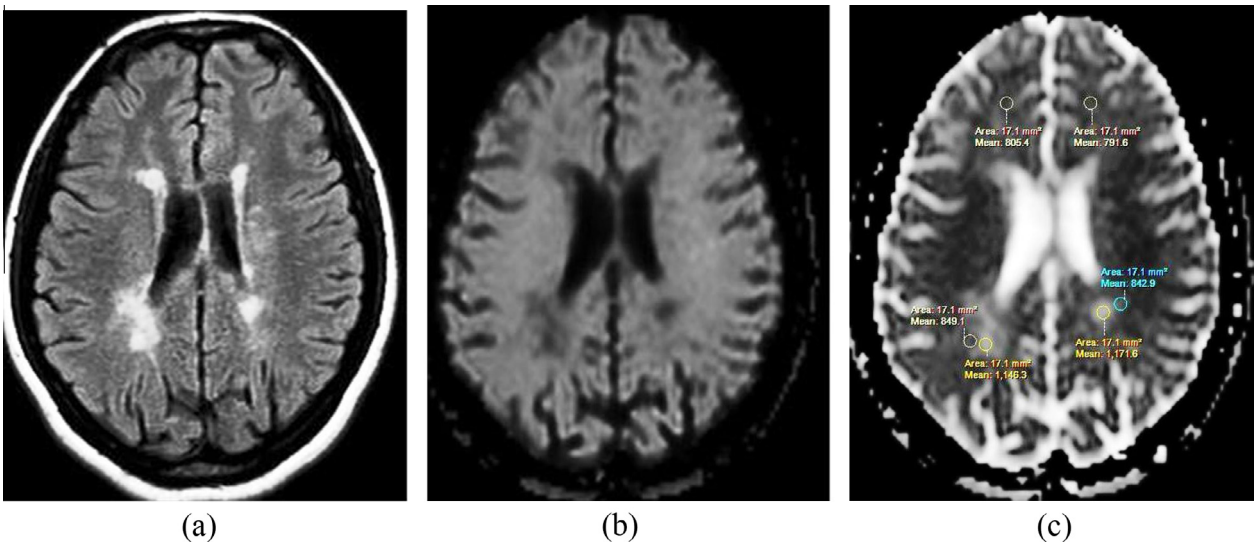


Fig. 6 40-year-old female patient with RRMS and no cognitive impairment (MOCA score 26). (a) Axial FLAIR showed multiple plaques, (b) DWI image showed signal intensity of facilitated diffusion, (c) ADC map showed the following readings: Plaque 1.1643×10^{-3}, Periplaque 0.8491×10^{-3} and NAWM 0.8054×10^{-3} mm^2/s.

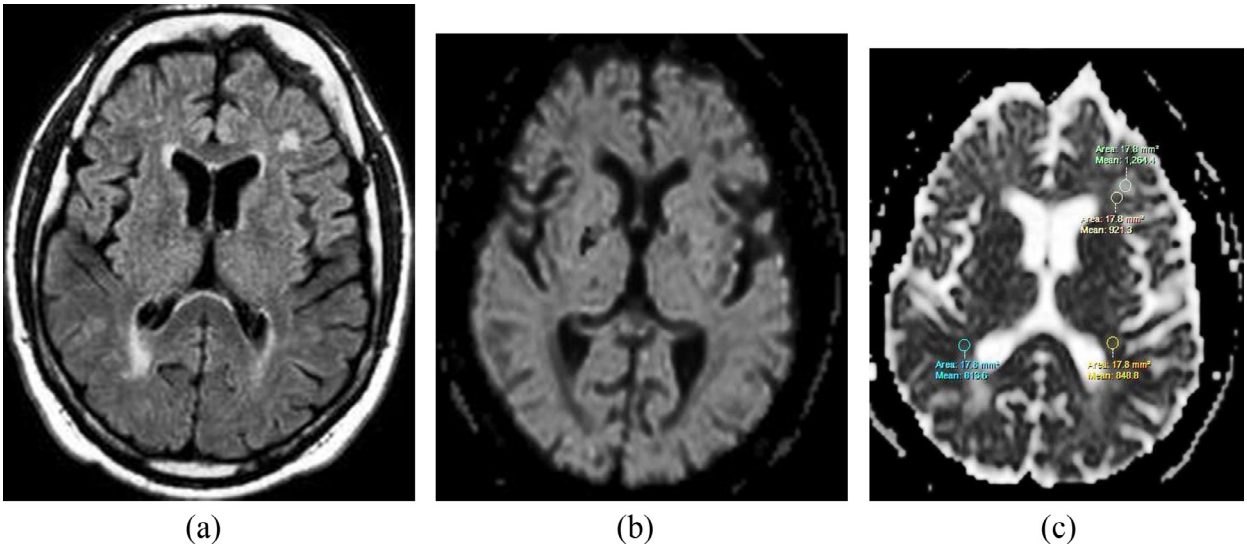


Fig. 7 39 year old male patient with RRMS and mild cognitive impairment (MOCA score 19). (a) Axial FLAIR showed multiple plaques, (b) DWI image showed signal intensity of facilitated diffusion, (c) ADC map showed the following readings: Plaque 1.2644×10^{-3}, Periplaque 0.9213×10^{-3}, and NAWM 0.8488×10^{-3} mm^2/s.

Table 3 The mean ADC values (ADC $\times 10^{-3}$ mm^2/s) in plaque, peri-plaque and NAWM in the 3 different groups.

	MS group with normal cognition mean ± SD	MS group with cognitive impairment mean ± SD	Control group mean ± SD	*P*
Plaque	1.198 ± 0.19	1.225 ± 0.6	–	0.85
Peri-plaque white matter	0.837 ± 0.03	0.939 ± 0.03	–	$<0.001^{**}$
NAWM	0.796 ± 0.03	0.819 ± 0.15	0.715 ± 0.2	0.51^{A} 0.08^{B} $0.05^{*,C}$
F	53.16	53.78		
P	$<0.001^{**}$	$<0.001^{**}$		
LSD	$<0.001^{**,a}$ $<0.001^{**,b}$ $0.02^{*,c}$	$<0.001^{**,a}$ $<0.001^{**,b}$ 0.10^{c}		

$^{*}p \leqslant 0.05$ (significant); $^{**}p \leqslant 0.01$ (highly significant).
[A] MS with normal cognition versus MS with impaired cognition.
[B] MS with normal cognition versus control.
[C] MS with impaired cognition versus control.
[a] Plaque versus Peri-plaque white matter.
[b] Plaque versus NAWM.
[c] Peri-plaque white matter versus NAWM.

Table 4 Correlation results between ADC value in plaque, periplaque and NAWM and cognition in the three groups.

Mean ADC	MS group with normal cognition		MS group with Cognitive impairment		Control group	
	r	*p*	*r*	*p*	*r*	*p*
Plaque	0.15	0.07 NS	−0.22	0.06	–	–
Peri-plaque white matter	0.12	0.12 NS	−0.64	$<0.001^{**}$	–	–
NAWM	0.16	0.06 NS	−0.56	0.01^{*}	0.09	0.27 NS

($r = -0.56$, $p = 0.01$). No significant correlation was found between the mean ADC in plaque and MOCA scores ($r = -0.22$, $p = 0.06$). Correlation results of the three groups are demonstrated in Table 4 and Fig. 8.

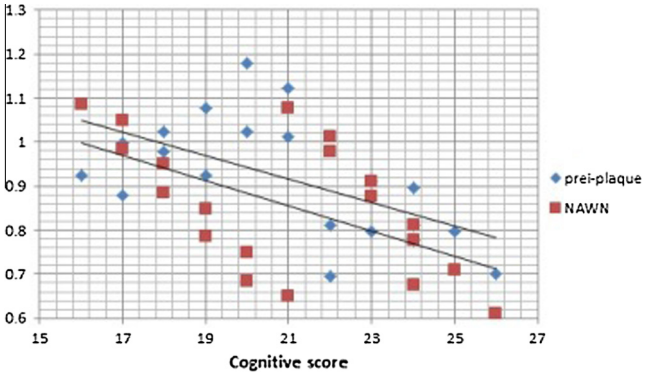


Fig. 8 Line graph shows correlation between ADC in peri-plaque and NAWM and MOCA score in MS group with cognitive impairment.

4. Discussion

MR imaging is the first imaging modality for diagnosis and follow-up of MS patients. The study of conventional MR imaging alone is limited and has low specificity since areas of edema, inflammation, gliosis, demyelination and axonal loss display high signal on T2 WIs and FLAIR sequences. In addition, conventional MR imaging has a low ability to determine the severity and extension of microscopic injuries on the NAWM surrounding the plaques (11–14).

Demyelination is the primary pathological course in MS (15). So quantitative information related to myelin destruction may be calculated with DWI and the ADC maps, which reflect the movement of water molecules in tissues (16,17).

In MS patients, ADC values of plaques and NAWM detected on T2-WI and FLAIR were significantly higher than the healthy control group (16–18). Guo et al. (12) found abnormal ADC values in all assessed white matter regions in MS patients included in their study (12–19). This was similar to our results as we found that, the mean ADC value of the NAWM ($0.819 \pm 0.15 \times 10^{-3}$ & $0.7962 \pm 0.03 \times 10^{-3}$ mm^2/s) in MS patients (with and without cognitive impairment respectively) was higher than mean ADC of the control group ($0.7154 \pm 0.2 \times 10^{-3}$ mm^2/s), with a significant difference between the MS patients with cognitive impairment and the control group ($p < 0.05$).

Guo et al. (19) also reported that the mean ADC of the plaque was (0.901 ± 0.095) $\times 10^{-3}$ mm^2/s with statistically significant differences between plaques and peri-plaque regions ($p < 0.001$) and between plaques and NAWM ($p < 0.001$). Also, in our study, we found that the mean ADC value of the plaque in the two MS groups was the highest ($1.198 \pm 0.19 \times 10^{-3}$ mm^2/s) and ($1.225 \pm 0.6 \times 10^{-3}$ mm^2/s) with a significant difference ($p < 0.001$) between plaques and each of the peri-plaque and NAWM.

ADC value in the peri-plaque region can be used as an indicator of WM integrity and the risk of developing or deterioration of the cognitive state. In agreement with other hypotheses

and histological supports of the extension of MS lesions beyond the plaques (14,20–22) we found that the mean ADC values in the peri-plaque regions in both MS groups (0.939 ± 0.03 & $0.837 \pm 0.03 \times 10^{-3}$ mm^2/s) were higher than mean ADC of the NAWM ($0.7154 \pm 0.2 \times 10^{-3}$ mm^2/s) in control group with significant difference ($p < 0.001$) only in the MS patient with cognitive impairment.

However in studies by Ge et al. (23) and Caramia et al. (24) they found no increase in the mean ADC in NAWM in MS patient, and the difference between these studies and ours may be attributed to the small number of the patients included in the first study (only 15) (23) or exposure of the patients to a single attack in the second study (24).

Neurocognitive dysfunction in MS patients has been reported to occur in approximately 40–70% (25–27). This was coping with our study as the cognitive impairment was detected in 44.4% of our MS patients according to MOCA scale and showed a significant difference between MS without cognitive impairment and control groups.

In MS patients, cognitive impairment has been reported in all stages of the disease, so early diagnosis of cognitive impairment is important, as it can predict the rate of disease progression, and help the patients to accept different disease-modifying treatments (28–30).

Other studies had proved a significant correlation between the cognitive performance and NABT in many diseases (31). Baseline findings from multinational Leukoaraiosis and Disability study (LADIS) (32) had reported that in NABT, DWI metrics are significantly associated with cognitive performance, but not within white matter hyperintensities

In agreement with many similar studies (26,33–35), we found that all the cognitive functions (visuospatial, executive, attention, memory, fluency and orientation) were impaired with a significant p-value (p value < 0.05) only in MS patients with cognitive impairment.

A moderate correlation among normal-appearing brain tissue, both white and gray matter and cognitive testing was found by DT-MRI techniques (4). In accordant with our study, in MS patient with cognitive impairment, there was an inverse (−ve) correlation with the mean ADC value in the peri-plaque and cognitive state according to MOCA scores ($r = -0.64$, $p < 0.001$). The less significant inverse correlation was found between the mean ADC values of NAWM and MOCA scores ($r = -0.56$, $p < 0.01$). No significant correlation was found between the ADC of plaque and MOCA scores ($r = -0.22$, $p < 0.06$).

Because of limited acquisitions in our institute, we used only the mean ADC from DW-MRI as an indicator of cell destruction and water diffusivity and ignored measuring the neural integrity via fractional anisotropy. We did not study the association between each individual cognitive function and mean ADC value, and also, there was no statistical analysis of the most affected cognitive function.

5. Conclusions

Hidden microstructural pathological changes in NAWM of MS patients can be detected by new imaging techniques such as DW-MRI. ADC values can be used as an useful biomarker to monitor the extent of brain damage Correlations between cognitive dysfunction and neuroimaging parameters, such as mean ADC, can predict MS patients susceptible to cognitive dysfunction and so modify the disease course.

Conflict of interest

The authors declare that there are no conflicts of interest.

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